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(54) **Purine derivatives, process for their preparation, pharmaceutical compositions and intermediates**

Purinverbindungen, Verfahren zu ihrer Herstellung, pharmazeutische Präparate und Zwischenverbindungen

Dérivés de purine, procédé pour leur préparation, compositions pharmaceutiques et intermédiaires

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- **CHEMICAL ABSTRACTS, vol. 109, no. 15, 10th October 1988, page 749, abstract no. 129567p, Columbus, Ohio, US; M.R. HARNDEN et al.: "Synthesis of 9-(3-hydroxypropoxy)guanine, a novel antiviral acyclonucleoside" & TETRAHEDRON LETT. 1988, 29(6), 701-4**

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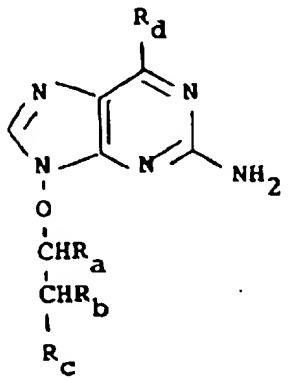
Description

The present invention relates to novel compounds which are of potential use as antiviral agents, to a process for their preparation and to their use as pharmaceuticals.

EP-A-242482 (Beecham Group p.l.c.), the subject matter of which is incorporated herein by reference, discloses antiviral compounds of formula (A) and pharmaceutically acceptable salts thereof:



(A)

wherein

R_a is hydrogen or CH_2OH;
R_b is hydrogen or, (when R_1 is hydrogen), hydroxy or CH_2OH;
R_c is CH_2OH or, (when R_1 and R_2 are both hydrogen), $CH(OH)CH_2OH$;
R_d is hydrogen, hydroxy, amino or OR_e

wherein

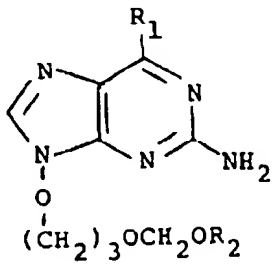
R_e is C_{1-6} alkyl, phenyl or phenyl C_{1-2} alkyl either of which phenyl moieties may be substituted by one or two halo, C_{1-4} alkyl or C_{1-4} alkoxy groups;

and in which any OH groups in R_a, R_b and/or R_c may be in the form of O-acyl, phosphate, cyclic acetal or cyclic carbonate derivatives thereof.

Compounds wherein R_d is other than hydroxy are pro-drugs for the compounds of formula (A) wherein R_d is hydroxy. Example 1 describes the compound of formula (I) wherein R_a and R_b are both hydrogen, R_c is CH_2OH and R_d is hydroxy which is 9-(3-hydroxyprop-1-oxy)guanine, hereinafter referred to as E1.

It has now been discovered that certain derivatives of E1 are pro-drugs for E1, having improved gastrointestinal absorption properties.

Accordingly, the present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein

R_1 is hydrogen or hydroxy; and

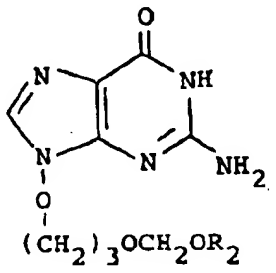
R_2 is C_{1-6} alkyl.

Suitable values for R_2 alkyl groups include methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl and pentyl (all possible isomers), particularly iso-propyl.

Pharmaceutically acceptable salts are as described in EP-A-242482.

The compounds of formula (I) including their alkali metal salts may form solvates such as hydrates and these are included wherever a compound of formula (I) or a salt thereof is herein referred to.

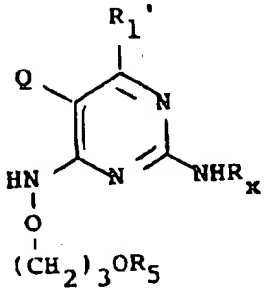
It will be appreciated that, when R_1 is hydroxy in formula (I) the compound exists in the predominant tautomeric form of structure (IA):



(IA)

The invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises either

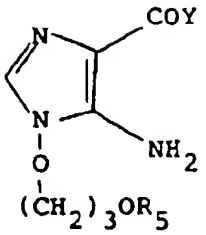
i) imidazole ring closure of a compound of formula (II):



(II)

wherein Q is a group capable of cyclising to form an imidazole ring, such as amino or an amino derivative, for example, formylamino; or

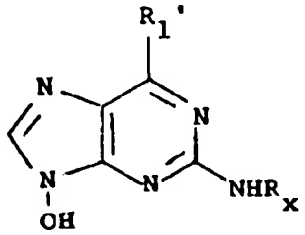
ii) pyrimidine ring closure of a compound of formula (III):



(III)

wherein Y is amino or C_{1-6} alkoxy, with a condensing agent capable of cyclising to form a pyrimidine ring having a 2-NHR_x substituent, resulting in a compound of formula (I) wherein R_1 is hydroxy; or

iii) condensing a compound of formula (IV):



(IV)

with a side chain intermediate of formula (V):

$$R_5O(CH_2)_3Z \qquad (V)$$

wherein Z is a leaving group;
and wherein, in formulae (II) to (V), R_5 is CH_2OR_2 or a group or atom convertible thereto, R_1' is R_1 or a group or atom convertible thereto, R_x is hydrogen or an amino protecting group; and thereafter, when desired or necessary, converting R_5 and/or R_1', when other than CH_2OR_2 and/or R_1, to CH_2OR_2 and/or R_1 respectively, and/or converting R_5 and/or R_1 when CH_2OR_2 and/or R_1 to other CH_2OR_2 and/or R_1 and/or converting R_x when an amino protecting group, to hydrogen.

Process i) may be carried out, preferably when Q is formylamino, using a cyclisation condensing agent, such as diethoxymethyl acetate or triethyl orthoformate, or by fusion.

Process ii) is preferably carried out in accordance with the methods described in EP-A-242482, the subject matter of which is incorporated herein by reference.

Process iii) may be carried out with suitable values for Z including hydroxy and halo, such as chloro, bromo and iodo, preferably iodo; or other groups readily displaceable by nucleophiles, such as mesyloxy or tosyloxy. The reaction preferably takes place in an inert solvent, such as dimethylformamide at 0-50°C, preferably ambient temperature. When Z is hydroxy, the reaction takes place in the presence of a dehydrating agent, such as diethyl azodicarboxylate in the presence of triphenylphosphine. When Z is halo, the reaction preferably takes place in the presence of a base, such as potassium carbonate.

Examples of conversions of variable groups are as follows:

$\underline{R_1'\text{-}R_1}$

a) An R_1 hydroxy group may be converted to R_1' is chloro, by chlorination using a reagent such as phosphorus oxychloride, preferably in the presence of tetraethylammonium chloride and dimethylaniline (as acid acceptor) in

CH_3CN at reflux temperatures, according to the method described by M.J. Robins and B. Ozanski, Can. J. Chem, 59, 2601 (1981).

b) When R_5 is other than CH_2OR_2, an R_1' chloro group may be converted to R_1 is hydroxy by hydrolysis using aqueous mineral acid, such as hydrochloric acid, or more preferably, using an organic acid, such as formic acid at elevated temperature, suitably 70-150°C, preferably around 100°C.

c) An R_1' chloro group may be converted to R_1' is methoxy by reaction with sodium methoxide. The R_1' is methoxy group may in turn be converted to R_1' is hydroxy by hydrolysis using non-acidic methods, preferably using mercaptoethanol.

d) An R_1' alkoxy group, such as methoxy, may also be converted to R_1 hydroxy by the methods of D.R. Haines, J. Med. Chem. 1987, 30, 943 and K.K. Ogilvie and H.R. Hanna, Can. J. Chem. 1984, 62, 2702.

R_5-CH_2OR_2

a) R_5 hydrogen may be converted to CH_2OR_2 by conventional procedures for preparing acetals, using LCH_2OR_2 wherein L is a leaving group, such as chloro or acetate.

b) R_5 hydrogen may be replaced by a protecting group, which may be removed by conventional deprotection methods, and then subsequently converted to CH_2OR_2 as in a) above.

Suitable examples of protecting groups and processes for their removal, are as described in EP-A-242482. Particularly suitable protecting groups include the benzyl group, removed by catalytic hydrogenation; the acetate group removed by acid hydrolysis, 2M HCl in ethanol; or the t-butyldimethylsilyl group removable by 80% acetic acid at elevated temperature, around 90°C.

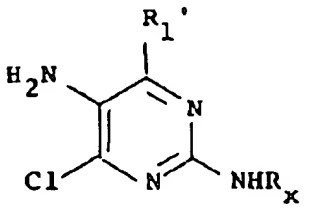
R_x'-R_x

R_x' may be formyl, which may be converted to R_x is hydrogen by hydrolysis, preferably under basic conditions.

It will be appreciated that the above conversions may take place in any desired or necessary order, having regard to the final desired compound of formula (I), and that interconversions involving acid conditions could affect the OCH_2OR_2 moiety in formula (I).

It is normally preferred that R_5 in the aforedescribed processes is CH_2OR_2 as defined.

Intermediates of formula (II) may be prepared from a corresponding compound of formula (VI):



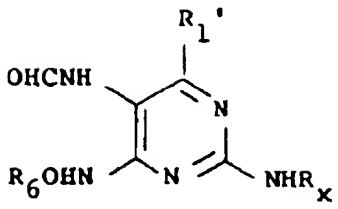
(VI)

and via intermediates of formula (V) wherein Z is OH, as hereinbefore defined, according to the methods described in EP-A-242482 i.e. by converting the compound of formula (V) wherein Z is OH to the phthalimidooxy derivative followed by reaction with methylhydrazine, as described in the Descriptions hereinafter.

The compound of formula (VI) wherein R_1' is chloro and R_x is hydrogen, is a known compound as described by Temple et. al., J. Org. Chem., 40 (21), 3141, 1975.

Intermediates of formula (III) may be prepared according to the methods described in EP-A-242482.

Compounds of the formula (IV) are prepared as described in EP-A-313289 (Beecham Group p.l.c.) from compounds of formula (VI) wherein the 5-amino group is formylated, by reaction with R_6ONH_2 wherein R_6 is a protecting group, to give a compound of formula (VII):



(VII)

which may be cyclised with diethoxymethyl acetate, to give a compound of formula (IV) wherein the OH group is protected. Suitable values for R_6 include benzyl, removable by hydrogenation, and the tetrahydropyran-2-yl group removable by treatment with 80% acetic acid, at ambient temperature.

Intermediates of the formula (V) wherein Z is hydroxy are known compounds or are prepared by analogous methods to those used for structurally similar known compounds.

Intermediates of formulae (II), (III) and (V) but wherein Z is replaced by an aminooxy group, and wherein R_5 is CH_2OR_2, are believed to be novel and form an aspect of the invention.

Pharmaceutically acceptable salts may be prepared in conventional manner, for example, in the case of acid addition salts, by reaction with the appropriate organic or inorganic acid.

The compounds of the invention are of potential use in the treatment of infections caused by viruses, especially herpesviruses such as herpes simplex type 1, herpes simplex type 2, varicella-zoster and Epstein-Barr virus.

Compounds of the invention may be formulated for use in a pharmaceutical composition. Accordingly, in a further aspect of the invention, there is provided a pharmaceutical composition which comprises a compound of formula (I) or pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or excipient.

A composition which may be administered by the oral route to humans may be compounded in the form of a syrup, tablet or capsule. When the composition is in the form of a tablet, any pharmaceutical carrier suitable for formulating such solid compositions may be used, for example magnesium stearate, starch, lactose, glucose, rice, flour and chalk. The composition may also be in the form of an ingestible capsule, for example of gelatin, to contain the compound, or in the form of a syrup, a solution or a suspension. Suitable liquid pharmaceutical carriers include ethyl alcohol, glycerine, saline and water to which flavouring or colouring agents may be added to form syrups. The compounds may also be presented with a sterile liquid carrier for injection.

The composition may also be formulated for topical application to the skin or eyes.

For topical application to the skin, the composition may be in the form of a cream, lotion or ointment. These formulations may be conventional formulations well known in the art, for example, as described in standard books of pharmaceutics and cosmetics, such as Harry's Cosmeticology published by Leonard Hill Books and the British Pharmacopaeia.

The composition for application to the eyes may be a conventional eye-drop composition well known in the art, or an ointment composition.

Preferably, the composition of this invention is in unit dosage form or in some other form that may be administered in a single dose. A suitable dosage unit might contain from 50 mg to 1 g of active ingredient, for example 100 to 500 mg.

Such doses may be administered 1 to 4 times a day or more usually 2 or 3 times a day. The effective dose of compound will in general be in the range of from 1.0 to 20 mg/kg of body weight per day or more usually 2.0 to 10 mg/kg per day.

No unacceptable toxicological effects are indicated at the above described dosage levels.

The invention also provides a method of treating viral infections in a human or non-human animal, which comprises administering to the animal an effective, non-toxic amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for the treatment of viral infections.

The compounds of the invention are also believed to exhibit a synergistic antiviral effect in conjunction with interferons; and combination products comprising these two components for sequential or concomitant administration, by the same or different routes, are therefore within the ambit of the present invention.

The following examples illustrate the invention; the following descriptions illustrate the preparation of intermediates.

Description 1 (Intermediates for Example 1)

a) 3-(Isopropoxymethoxy)propanol

A solution of 1,3-propanediol (19.4g, 255mmol) in dry tetrahydrofuran (100ml) under nitrogen at 0-5°C was treated with sodium hydride (2.04g, 85mmol) and stirred for 1 hour. Chloromethylisopropyl ether (9g, 83mmol) in dry tetrahydrofuran (15ml) was added over 15 min. Stirring was continued for a further 2 hours. The reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica eluting with dichloromethane: methanol (97:4) to give the title compound as a colourless oil. (5.3g, 44%). ν_{max} (Film) 3400, 2910, 2860, 2805, 2760, 1460, 1440, 1425, 1410 and 1380cm^{-1}; δ_H ($CDCl_3$) 1.17 (3H, s, CH_3), 1.20 (3H, s,CH_3), 1.84 (2H, quintet, J=6Hz $CH_2\underline{CH_2}CH_2$), 2.3 (1H, br s, D_2O exchangeable OH), 3.72 (2H, t, J=6Hz, $\underline{CH_2}OCH_2OCH(CH_3)_2$) 3.76 (2H, t, J=6Hz,$CH_2ON$), 3.86 (1H, m, $CH(CH_3)_2$), 4.70 (2H, s, OCH_2O).

b) N-[3-(Isopropoxymethoxy)propoxy]phthalimide

A mixture of [3-(isopropoxymethoxy)propanol (5.3g, 35.6mmol), N-hydroxyphthalimide (5.83g, 35.8mmol) and triphenylphosphine (10.48g, 40mmol) in dry tetrahydrofuran (75ml) at 0-5°C; was treated with a solution of diethyl azodicarboxylate (6.96g, 40mmol) in dry tetrahydrofuran (15ml) over 15min. The reaction mixture was stirred at ambient temperature for 18hr. The solvent was removed in vacuo and the residue was dissolved in diethyl ether (100ml) and cooled to 5°C for 2hr. The solid was filtered off, the filtrate evaporated in vacuo, and the residue purified by column chromatography on silica eluting with hexane: ethyl acetate (70:30) to give the title compound as an oil (9.3g, 88%). ν_{max} (Film) 2980, 2940, 2900, 1740, 1475 and 1380 cm^{-1}; δ_H ($CDCl_3$) 1.17 (3H, s, CH_3), 1.19 (3H, s, CH_3), 2.06 (2H, quintet, J=6.3Hz $CH_2\underline{CH_2}CH_2$), 3.77 (2H, t, J=6.3Hz, $\underline{CH_2}OCH_2OCH(CH_3)_2$), 3.88 (1H, septet, J=6.3Hz, $OCH(CH_3)_2$), 4.32 (2H, t, J=6.3Hz CH_2ON), 4.73 (2H, s, OCH_2O), 7.78 (4H, m, ArH). (Found: C, 16.53; H, 6.59; N, 4.71%: $C_{15}H_{19}NO_5$ requires: C, 16.42; H, 6.52; N, 4.77%).

c) N-[3-(Isopropoxymethoxy)propoxyamine

A solution of N-[3-(isopropoxymethoxy)propoxy]phthalimide (9.3g, 31.7mmol) in dry dichloromethane (70ml) at ambient temperature was treated with N-methylhydrazine (2.2g, 47.8mmol) and stirred for 2 hours. The reaction mixture was filtered, the filtrate evaporated in vacuo and the residue purified by column chromatography on silica eluting with hexane: ethyl acetate (60:40) to give the title compound as a colourless oil (4.2g, 82%). ν_{max} (Film) 3310, 3220, 3160, 2960, 2920, 2870, 1580, 1465 and 1380 cm^{-1}; δ_H ($CDCl_3$) 1.10 (3H, s, CH_3), 1.18 (3H, s, CH_3), 1.80 (2H, quintet, J=6.3Hz $CH_2\underline{CH_2}CH_2$), 3.52 (2H, t, J=6.3Hz, $\underline{CH_2}OCH_2OCH(CH_3)_2$), 3.66 (2H, t, J=6.3Hz, CH_2ON), 3.8 (1H, septet, J=6.3Hz $OCH(CH_3)_2$), 4.65, (2H, s, OCH_2O), 5.2-55 (2H, br s, D_2O exchangeable NH_2).

d) 4-Chloro-2,5-diformamido-6-[(3-isopropoxymethoxy)propoxy]aminopyrimidine

A mixture of 4,6-dichloro-2,5-diformamidopyrimidine (2.9g, 12.3mmol), 3-(isopropoxymethoxy)propoxyamine (2.0g, 12.2mmol) and N,N-diisopropylethylamine (4.3ml, 3.19g, 24.6mmol) in diglyme (50ml) was heated to 100° for 3hr. The cooled reaction mixture was filtered, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica eluting with ethyl acetate:hexane (1:1) then ethyl acetate to give the title compound as a yellow gum, which crystallised from ethyl acetate (3.0g, 75%) mp 132.4°C. ν_{max}(KBr) 3250, 2960, 2910, 2870, 1705, 1645, 1590, 1565, 1495, 1460 and 1380cm^{-1}; δH [$(CD_3)_2SO$]: 1.08 (3H, s, CH_3), 1.10 (3H, s, CH_3), 1.84 (2H, quintet, J=6.3 Hz, $CH_2CH_2CH_2$), 3.58 (2H, t, J 6.3 Hz, $\underline{CH_2}OCH_2OCH(CH_3)_2$), 3.76 (1H, septet, J=6.3 Hz, $OCH(CH_3)_2$), 3.93 (2H, t, J 6.3 Hz, CH_2ON), 4.61 (2H, s, OCH_2O), 8.14 (1H, s, NHC<u>H</u>O), 9.25 (1H, br.s, NHC<u>H</u>O), 9.39 (1H, br.s, D_2O exchangeable N<u>H</u>OCH_2), 10.6-11.0 (2H, br, D_2O exchangeable, 2 x N<u>H</u>CHO). (Found: C, 43.20; H, 5.55; N, 19.24%. $C_{13}H_{20}N_5O_5Cl$ requires: C, 43.15; H, 5.57; N, 19.35%).

Description 2 (Intermediates for Example 2)

a) 3-(Methoxymethoxy)propanol

A solution of 1,3-propanediol (25.1g, 330mmol) in dry tetrahydrofuran (10ml) was treated with sodium hydride (80%, 3.3g, 110mmol) at room temperature under nitrogen. The solution was stirred at ambient temperature for 30min. then chloromethylmethyl ether (8.85g, 110mmol) was added dropwise with stirring in dry tetrahydrofuran (15ml), maintaining the temperature at 10°C (ice bath). The reaction was stirred for 2hr. then filtered and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica eluting with dichloromethane: methanol (97:

3) to give the title compound as a colourless oil (7.0g, 53%). ν_{max}(Film) 3400, 2920, 2880, 2760, 1460, 1435, and 1380cm^{-1}; δ_H($CDCl_3$) 1.9 (2H, quintet, J=6Hz, $CH_2\underline{CH_2}CH_2$), 3.1 (1H, s, D_2O exchangeable, OH), 3.35 (3H, s, OCH_3), 3.7 (4H, m, $\underline{CH_2}OH$, $\underline{CH_2}OCH_2OCH_3$), 4.65 (2H, s, OCH_2O).

b) N-[3-(Methoxymethoxy)propoxy]phthalimide

A solution of 3-(methoxymethoxy)propanol (5g, 41.6mmol), triphenylphosphine (13.1g, 50mmol) and N-hydroxyphthalimide (7.25g, 44mmol) in dry tetrahydrofuran (150ml) was cooled to 0-5°C and treated with diethyl azodicarboxylate (8.7g, 50mmol) in dry tetrahydrofuran (10ml) over ½hr. The reaction was then stirred at ambient temperature for 18hr. The solvent was removed in vacuo and the residue was dissolved in diethyl ether (100ml) and the mixture cooled to 0-5°C for 3hr. The solid was removed by filtration and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica eluting with hexane: ethyl acetate (70:30) to give the title compound as an oil (4.5g, 41%). ν_{max}(Film) 2960, 2900, 1800, 1740, 1620, 1480 and 1380cm^{-1}; δ_H($CDCl_3$) 2.07 (2H, quintet, J=6.3 Hz, $CH_2\underline{CH_2}CH_2$), 3.38 (3H, s, OCH_3), 3.77 (2H, t, J=6.3 Hz, $\underline{CH_2}OCH_2OCH_3$), 4.33 (2H, t, J=6.3 Hz, CH_2ON), 4.66 (2H, s, OCH_2O), 7.83 (4H, m, ArH).

c) 3-Methoxymethoxypropoxyamine

A solution of N[3-(methoxymethoxy)propoxy]phthalimide (4.5g, 17mmol) in dry dichloromethane (50ml) was cooled to 0-5° and treated with N-methylhydrazine (1.2g, 26mmol). The reaction mixture was stirred for 2hr then filtered and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica eluting with hexane: ethyl acetate (60:40) to give the title compound as a colourless oil (1.1g, 50%). ν_{max} (Film) 3310, 3240, 3160, 2960, 2910, 1590, 1465, and 1380cm^{-1}; δ_H($CDCl_3$) 2.07 (2H, quintet, J=6.3Hz, $CH_2\underline{CH_2}CH_2$), 3.38 (3H, s, CH_3O), 3.50 (2H, t, J=6.3Hz, $\underline{CH_2}OCH_2OCH_3$), 3.70 (2H, t, J 6.3 Hz, $\underline{CH_2}ONH_2$), 4.66 (2H, s, OCH_2O), 5.2-5.5 (2H, br.s, D_2O exchangeable, NH_2).

d) 4-Chloro-6-[3-(methoxymethoxy)propoxy]amino-2,5-diformamidopyrimidine

A mixture of 4,6-dichloro-2,5-diformamidopyrimidine (1.75g, 7.4mmol), 3-(methoxymethoxy)propoxyamine (1.0g, 7.4mmol) and N,N-diisopropylethylamine (2g, 15.5mmol) in dry diglyme was heated to 100°C for 2hr. The cooled reaction mixture was filtered and the filtrate was evaporated in vacuo. The residue was purified by column chromatography on silica eluting with ethyl acetate:hexane (50:50) then ethyl acetate to give the title compound as a yellow oil which was crystallised from ethyl acetate (1.2g, 50%) mp 136-8°C. ν_{max}(KBr) 3240, 2920, 2880, 1705, 1640, 1590, 1565, 1495, 14650, 1410, and 1380cm^{-1}; δ_H [$(CD_3)_2SO$] 1.85 (2H, quintet, J=6.3Hz, $CH_2\underline{CH_2}CH_2$), 3.24 (3H, s, OCH_3), 3.58 (2H, t, J=6.3Hz, $\underline{CH_2}OCH_2OCH_3$), 3.94 (2H, t, J=6.3Hz, $\underline{CH_2}ONH$), 4.5 (2H, s, OCH_2O), 8.15 (1H, s, NHC<u>H</u>O), 9.26 (1H, d, J=9.6Hz, collapses to singlet on D_2O, NHC<u>H</u>O), 9.4 (1H, s, D_2O exchangeable N<u>H</u>OCH_2), 10.73 (1H, s, D_2O, exchangeable N<u>H</u>CHO), 10.84 (1H, d, J=9.6Hz, D_2O exchangeable, N<u>H</u>CHO).

Description 3 (Intermediate for Examples 4 and 5)

3-(Ethoxymethoxy)propan-1-ol

A solution of chloroethylethyl ether (50mmol) in dry tetrahydrofuran (10ml) was added dropwise at 0-5°C to a stirred solution of 1,3-propanediol (150mmol) in dry tetrahydrofuran (100ml) and N,N-diisopropylethylamine (75mmol). The mixture was stirred for 2 hours at room temperature, the solvent was evaporated in vacuo and the residue was purified by column chromatography on silica, eluting with dichloromethane:methanol (98:2) to give the title compound as a colourless oil (5.6g, 83%); ν_{max}(Film) 3420, 2980, 2940, 2880, 1480, 1445, 1390 and 1180 cm^{-1}; δ_H($CDCl_3$) 1.20 (3H, t, J=6.5Hz, $\underline{CH_3}CH_2$), 1.8 (2H, m, $CH_2\underline{CH_2}CH_2$), 3.2 (1H, s, OH), 3.6 (6H, m, $\underline{CH_2}OH$, CH_2O and $CH_3\underline{CH_2}$), 4.8 (2H, s, OCH_2O).

Examples

The following compounds of formula (I) were prepared.

Example No	R_1	R_2
1	H	$(CH_3)_2CH$
2	H	CH_3

(continued)

Example No	R_1	R_2
3	OH	$(CH_3)_2CH$
4	OH	C_2H_5
5	H	C_2H_5

Example 1

2-Amino-9-[3-(isopropoxymethoxy)propoxy)purine

a) A mixture of 4-chloro-2,5-diformamido-6-[3-(isopropoxymethoxy)propoxyamino]pyrimidine (3.3g, 9.12mmol) and diethoxymethyl acetate (10ml) was heated at 120°C for 1hr. The solution was then evaporated and the residue taken up into methanol (30ml) and concentrated aqueous ammonia (3ml). After 1hr. at 20°C the solvent was removed and the residue purified by column chromatography on silica gel eluting with hexane:ethyl acetate (1:1) to afford 6-chloro-2-formamido-9-[3-(isopropoxymethoxy)propoxy]purine (1.89g; 60%), ν_{max} (KBr) 2970, 1697, 1609, 1591, 1503, 1383cm^{-1}; δ_H [$(CD_3)_2SO$], 1.10 (6H, d, J=6.3Hz, 2 x CH_3), 1.97 (2H, quintet, J=6.3Hz, $CH_2\underline{CH_2}CH_2$), 3.67 (2H, t, J=6.3Hz, CH_2OC), 3.77 (1H, septet, J=6.3Hz, CH), 4.49 (2H, t, J=6.3Hz, CH_2ON), 4.65 (2H, s, $OC\underline{H_2}O$), 8.81 (1H, s, H-8), 9.37 (1H, d, J=9.1Hz, C<u>H</u>O), 11.30 (1H, br.s, J=9.1Hz, N<u>H</u>).

b) A mixture of 6-chloro-2-formamido-9-[3-(isopropoxymethoxy)propoxy]purine (1.86g, 5.40mmol), 10% palladium on charcoal (190mg), triethylamine (3.8ml, 27mmol) and methanol (30ml) was stirred under an atmosphere of hydrogen at 20°C for 4hr. The suspension was filtered, the catalyst washed with chloroform and the combined filtrates evaporated under reduced pressure. The residue was dissolved in dichloromethane (50ml), washed with saturated brine-water (2:1), dried (magnesium sulphate) and evaporated. The residue was dissolved in 0.5M sodium methoxide in methanol (21.6ml) and heated at reflux for 1hr. The solution was taken to neutrality using AMBERLITE IR 120(H) and evaporated. The residue was purified by column chromatography on silica gel eluting with chloroform-methanol (20:1) affording the title compound (600mg, 41%) after recrystallisation from acetone-hexane; ν_{max}(KBr) 3333, 3192, 1661, 1623, 1577, 1516, 1433 cm^{-1}; δ_H [$(CD_3)_2SO$] 1.09 (6H, d,J 6.05 Hz, 2 x CH_3), 1.95 (2H, quintet, J 6.6 and 6.3 Hz, $CH_2\underline{CH_2}CH_2$), 3.63 (2H, t, J=6.3Hz, $C\underline{H_2}OC$), 3.77 (1H, septet, J=6.0Hz, CH), 4.39 (2H, J=6.6Hz, CH_2ON), 4.64 (2H, s, OCH_2O), 6.69 (2H, br.s, D_2O exchangeable, NH_2), 8.31 (1H, s, H-8), 8.59 (1H, s, H-6). Found: C, 51.21; H, 6.84; N, 24.82%; $C_{12}H_{19}N_5O_3$ requires: C, 51.22; H, 6.82; N, 24.89%.

Example 2

2-Amino-9-[3-(methoxymethoxy)propoxyl]purine

a) A mixture of 4-chloro-2,5-diformamido-6-[3-(methoxymethoxy)propoxy]pyrimidine (1.2g, 3.80mmol) and diethoxymethyl acetate (10ml) was heated at 120°C for 1hr, then cooled and evaporated. The residue was taken up into methanol (10ml) and concentrated aqueous ammonia (1ml) and stirred at 20°C for 1hr. The solvent was then removed <u>in vacuo</u>. The residue was purified by column chromatography on silica gel eluting with ethyl acetate-hexane (1:1) affording 6-chloro-2-formamido-9-[3-(methoxymethoxy)propoxy]purine (0.45g, 1.42mmol) which was dissolved in methanol (30ml), and treated with excess triethylamine (1ml). The flask was flushed with nitrogen, palladium on carbon (10%, 40mg) was added and the mixture was hydrogenated at S.T.P. until hydrogen uptake ceased. The reaction mixture was filtered, the filtrate evaporated <u>in vacuo</u> and the residue purified by crystallisation from methanol to give 2-formamido-9-[3-(methoxymethoxy)propoxy]purine as colourless crystals (0.4g, 100%) mp. 115-116°C. λ_{max} (MeOH) 231 (ε 23,880), 255 (8120) and 290nm (9430); ν_{max}(KBr) 3120, 3070, 2930, 2810, 1690, 1610, 1510, 1445, 1410, and 1375cm^{-1}. δ_H[$(CD_3)_2SO$] 1.98 (2H, quintet, J=6.3Hz, $CH_2\underline{CH_2}CH_2$), 3.25 (3H, s, OCH_3), 3.67 (2H, t, J=6.3Hz, $C\underline{H_2}OCH_2OCH_3$), 4.5 (2H, t, J 6.3 Hz, CH_2ON), 4.58 (2H, s, OCH_2O), 8.73 (1H, s, 8-H), 8.98 (1H, s, 6-H), 9.42 (1H, d, J=9.6Hz, collapses to singlet on D_2O NHC<u>H</u>O), 11.1 (1H, d, J=9.6Hz, D_2O exchangeable N<u>H</u>CHO). (Found: C, 47.11; H, 5.27; N, 24.18%; $C_{11}H_{15}N_5O_4$ requires: C, 46.97; H, 5.37; N, 24.90%).

b) A solution of 2-formamido-9-[3-(methoxymethoxy)propoxy]purine (0.4g, 1.42mmol) in methanol (15ml) was treated with sodium methoxide solution (0.5M, 5ml) and heated to reflux for 2hr. The cooled reaction mixture was neutralised with AMBERLITE IR 120H resin, filtered and the solvent was removed <u>in vacuo</u>.

The residue was dissolved in ethyl acetate (50ml), washed with water (2 x 20ml), dried ($MgSO_4$), filtered and the filtrate evaporated in vacuo. The residue was purified by column chromatography on silica eluting with ethyl acetate, followed by crystallisation from acetone/hexane to give the title compound as colourless crystals (0.2g, 55%) mp 80-1°C. λ_{max} (MeOH) 223 (ε 26,375), 245 (5020) and 310 nm (7320); ν_{max}(KBr) 3320, 3180, 3080, 2940, 2880, 1645, 1610, 1580, 1505, 1465, and 1430cm^{-1}; δ_H [$(CD_3)_2SO$] 1.95 (2H, quintet, J=6.3Hz, $CH_2C\underline{H_2}CH_2$), 3.25 (3H, s, OCH_3), 3.63 (2H, t, J=6.3Hz, $C\underline{H_2}OCH_2OCH_3$), 4.40 (2H, t, J=6.3Hz, CH_2ON), 4.57 (2H, s, OCH_2O), 6.68 (2H, br.s, D_2O exchangeable NH_2), 8.3 (1H, s, 8-H), 8.59 (1H, s, 6-H). (Found: C, 47.34; H 6.08% $C_{10}H_{15}N_5O_3$ requires: C, 47.42; H, 59.7%).

Example 3

9-[3-(Isopropoxymethoxy)propoxy]guanine

a) Diethyl azodicarboxylate (1.24ml, 7.87mmol) was added to a cooled solution of 2-[(bis-t-butoxycarbonyl)amino]-9-hydroxy-6-methoxypurine (2.0g, 5.23mmol), 3-(isopropoxymethoxy)propanol (0.85g, 5.75mmol), and triphenylphosphine (2.06g, 7.87mmol) in THF (50ml). The reaction mixture was stirred for 16 hours, and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane-acetone, 3:1) affording 2-[(bis-t-butoxycarbonyl)amino]-9-[3-(isopropoxymethoxy)propoxy]-6-methoxypurine (2.23g, 83%). ν_{max} (KBr), 2975, 1786, 1761, 1597 and 1389 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.90 (6H, d, J=6.3Hz, 2xCH_3), 1.40 (18H, s, 6xCH_3), 1.96 (2H, quintet, J=6.3Hz, $OCH_2C\underline{H_2}CH_2O$), 3.64 (2H, t, J=6.3Hz, CH_2O), 3.78 (1H, quintet, J=6.3Hz, CHO), 4.08 (2H, s, OCH_3), 4.48 (2H, t, J=6.3Hz, CH_2ON), 4.63 (2H, s, OCH_2O), 8.74 (1H, s, H-8). (Found: C, 54.09; H, 7.59; N, 13.65%. $C_{23}H_{37}N_5O_8$ requires: C, 53.99; H, 7.30; N, 13.69%).

b) A solution of 2-[(bis-t-butoxycarbonyl)amino]-9-[3-(isopropoxymethoxy)propoxy]-6-methoxypurine in 0.5M sodium methoxide in methanol (33ml) was heated at reflux temperature for 16 hours. 2-Mercaptoethanol (1.3ml) was then added and the reaction mixture heated for a further 48 hours. The suspension was cooled, neutralised and evaporated to dryness. The residue was purified by reverse phase chromatography eluting with water then water-methanol-concentrated aqueous ammonia (10:1:1), to afford the title compound (390mg; 34%) after recrystallisation from water. ν_{max}(KBr) 3332, 3131, 3168, 1695, 1599, 1586 and 1384 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.09 (6H, d, J=6.1Hz, 2xCH_3), 1.91 (2H, quintet, J=6.6Hz, 6.3Hz, $OCH_2C\underline{H_2}CH_2O$), 3.61 (2H, t, J=6.3Hz, CH_2O), 3.77 (1H, septet, J=6.0Hz, CHO), 4.32 (2H, t, J=6.6Hz, CH_2ON), 4.63 (2H, s, OCH_2O), 6.58 (2H, br.s, NH_2), 7.93 (1H, s, H-8), 0.64 (1H, br.s, H-1). (Found: C, 48.58; H, 6.39; N, 23.44%. $C_{12}H_{19}N_5O_4$ requires C: 48.47; H, 6.45; N, 23.56%).

Example 4

9-[3-(Ethoxymethoxy)propoxy]guanine

a) A mixture of 2-[(bis-t-butoxycarbonyl)amino]-9-hydroxy-6-methoxypurine (2.85g, 7.48mmol), 3-(ethoxymethoxy)propan-1-ol (1.0g, 7.46mmol) and triphenylphosphine (2.62g, 10mmol) in dry tetrahydrofuran (50ml) was cooled to 0-5°C and treated with a solution of diethyl azodicarboxylate (1.74g, 10mmol) in dry tetrahydrofuran (10ml), the solution was then allowed to stand at room temperature overnight. The solvent was then removed in vacuo and the residue was purified by column chromatography on silica, eluting with hexane:acetone (95:5) to give 2-[(bis-t-butoxycarbonyl)amino]-9-[3-(ethoxymethoxy)propoxy]-6-methoxypurine as a yellow gum (1.7g, 46%). ν_{max}(Film) 3120, 2980, 2940, 2880, 1795, 1760, 1595, 1475, 1410, 1390, 1370, 1280 and 1255 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.10 (3H, t, J=6.8Hz, $C\underline{H_3}CH_2$), 1.4 (18H, s, CH_3x6), 1.96 (2H, m, J=6.3Hz, $CH_2C\underline{H_2}CH_2$), 3.47 (2H, q, J=6.8Hz, $CH_3C\underline{H_2}$), 3.64 (2H, t, J=6.3Hz, $CH_2C\underline{H_2}ON$), 4.07 (3H, s, OCH_3), 4.47 (2H, t, J=6.3Hz, $OC\underline{H_2}CH_2$), 4.6 (2H, s, OCH_2O), 8.74 (1H, s, 8-H). (Found: C, 52.57; H, 7.18; N, 13.92%; $C_{22}H_{35}N_5O_8$ requires: C, 53.10; H, 7.09; N, 14.07%) MS (70eV) m/z = 498 (MH^+).

b) A solution of 2-[(bis-t-butoxycarbonyl)amino]-9-[3-(ethoxymethoxy)propoxy]-6-methoxypurine (0.7g, 1.4mmol) in sodium methoxide (0.5M, 25ml) was heated to reflux for 18hr. 2-Mercaptoethanol (1ml) was then added to the solution and heating was continued for a further 18hr. The cooled reaction mixture was neutralised with hydrochloric acid solution (0.5M) and the solvent was removed in vacuo. The residue was purified by column chromatography on silica eluting with chloroform:methanol (90:10) followed by crystallisation from methanol to give the title compound as colourless crystals (0.1g, 25%) mp 242-5°C. λ_{max}(MeOH) 250nm (14080); ν_{max}(KBr) 3320, 3160, 2870, 2730, 1690, 1645, 1590, 1535, 1470, 1385 and 1320cm^{-1}; δ_H[$(CD_3)_2SO$] 1.11 (3H, t, J=7.1Hz, $CH_2C\underline{H_3}$), 1.92 (2H, m, J=6.5Hz, $CH_2C\underline{H_2}CH_2$), 3.5 (2H, q, J=7.1Hz, $C\underline{H_2}CH_3$), 3.61 (2H, t, J=6.3Hz, $CH_2C\underline{H_2}ON$), 4.32 (2H, t, J=6.3Hz, $OC\underline{H_2}CH_2$), 4.60 (2H, s, OCH_2O), 6.57 (2H, br.s, D_2O exchangeable, NH_2), 7.92 (1H, s, 8-H), 10.63 (1H, br.s, D_2O

exchangeable, NH). (Found: C, 46.64; H, 5.78; N, 24.55%; $C_{11}H_{17}N_5O_4$ requires: C, 46.63; H, 6.05; N, 24.72%) MS (70eV) m/z = 284 (MH^+).

Example 5

2-Amino-9-[3-(ethoxymethoxy)propoxy]purine

a) A solution of 2-[(bis-t-butoxycarbonyl)amino]-6-chloro-9-hydroxypurine (2.4g, 7.4mmol), 3-(ethoxymethoxy)propan-1-ol (1.0g, 7.4mmol) and triphenylphosphine (2.62g, 10mmol) in dry tetrahydrofuran (35ml) was cooled to 0-5°C and treated with a solution of diethyl azodicarboxylate (1.75g, 10mmol) in dry tetrahydrofuran (10ml). The solution was allowed to stand at room temperature overnight, the solvent was evaporated in vacuo and the residue purified by column chromatography on silica eluting with chloroform:methanol (98:2) followed by a further column eluting with hexane:acetone (90:10) to give 2-[(bis-t-butoxycarbonyl)amino]-6-chloro-9-[3-(ethoxymethoxy)propoxy]purine as a colourless gum (1.7g, 46%). ν_{max}(Film) 3100, 2980, 2930, 2880, 1795, 1760, 1600, 1560, 1425, 1370, 1280 and 1155cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.11 (3H, t, J=7.1Hz, $C\underline{H}_3CH_2$), 1.4 (18H, s, CH_3x6), 2.01 (2H, m, J=6.3Hz, $CH_2C\underline{H}_2CH_2$), 3.5 (2H, q, J=7.1Hz, $CH_3C\underline{H}_2$), 3.64 (2H, t, J=6.3Hz, $CH_2C\underline{H}_2ON$), 4.55 (2H, t, J=6.3Hz, $OC\underline{H}_2CH_2$), 4.6 (2H, s, OCH_2O), 9.08 (1H, s, 8-H). (Found: C, 50.28; H, 6.55; N, 13.70%; $C_{21}H_{32}N_5O_7Cl$ requires: C, 50.24; H, 6.42; N, 13.95%); MS (70eV) m/z = 502 (MH^+).

b) To a solution of 2-[(bis-t-butoxycarbonyl)amino]-6-chloro-9-[3-(ethoxymethoxy)propoxy]purine (1.5g, 2.98mmol) in methanol (25ml) and triethylamine (1ml) under a nitrogen atmosphere was added palladium on carbon (5%, 0.1g) and the mixture was hydrogenated at S.T.P. until hydrogen uptake ceased. The reaction mixture was filtered and evaporated in vacuo and the residue was purified by column chromatography on silica, eluting with ethyl acetate:hexane (50:50) to give 2-[(bis-t-butoxycarbonyl)amino]-9-[3-(ethoxymethoxy)propoxy]purine as a colourless gum. (1.2g, 86%). ν_{max}(Film) 3100, 2980, 2930, 2880, 1790, 1735, 1600, 1575, 1480, 1455, 1390, 1370, 1280 and 1250cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.11 (3H, t, J=7.1Hz, $CH_2C\underline{H}_3$), 1.38 (18H, s, CH_3x6), 1.98 (2H, m, J=6.3Hz, $CH_2C\underline{H}_2CH_2$), 3.5 (2H, q, J=7.1Hz, $C\underline{H}_2CH_3$), 3.65 (2H, t, J=6.3Hz, $CH_2C\underline{H}_2ON$), 4.52 (2H, t, J=6.3Hz, $OC\underline{H}_2CH_2$), 4.60 (2H, s, OCH_2O), 8.98 (1H, s, 8-H), 9.21 (1H, s, 6-H). (Found: C, 53.88; H, 7.26; N, 15.13%; $C_{21}H_{33}N_6O_7$ requires: C, 53.94, H, 7.11; N, 14.98%) MS (70eV) m/z = 468 (MH^+).

c) 2-[(Bis-t-butoxycarbonyl)amino]-9-[3-(ethoxymethoxy)propoxy]purine (0.5g, 1.07mmol) was dissolved in sodium methoxide solution (0.5M, 30ml) and heated to reflux for 18hr. The cooled reaction mixture was evaporated in vacuo and the residue was purified by column chromatography on silica, eluting with ethyl acetate:hexane (60:40) followed by crystallisation from acetone:hexane to give the title compound as colourless crystals (0.25g, 89%) mp 73-4°C. λ_{max}(MeOH) 224, 246 and 310nm. (5610, 3750 and 20,700); ν_{max}(KBr) 3370, 3330, 3200, 3080, 2930, 2880, 1645, 1615, 1570, 1505, 1475, 1425, 1320, 1280 and 1220cm^{-1}; $\delta_H[(CD_3)_2SO]$ 1.11 (3H, t, J=7.1Hz, $CH_2C\underline{H}_3$), 1.95 (2H, m, J=6.3Hz, $CH_2C\underline{H}_2CH_2$), 3.50 (2H, q, J=7.1Hz, $C\underline{H}_2CH_3$), 3.63 (2H, t, J=6.3Hz, $CH_2C\underline{H}_2ON$), 4.4 (2H, t, J=6.6Hz, $OC\underline{H}_2CH_2$), 4.61 (2H, s, OCH_2O), 6.69 (2H, br.s, D_2O exchangeable, NH_2), 8.31 (1H, s, 8-H), 8.59 (1H, s, 6-H). (Found: C, 49.48; H, 6.50; N, 26.33%; $C_{11}H_{17}N_5O_3$ requires: C, 49.42; H, 6.41; N, 26.20%); MS (70eV) m/z = 268 (MH^+).

Biological Evaluation

Procedure

Compounds were administered as single doses of 0.2mmole/kg in 0.1ml of 1% carboxymethyl cellulose by oral gavage to female Balb/c mice weighing 20g. Food was withheld from the mice for 18 hours prior to the start of the experiment. Blood was collected by cardiac puncture using heparinised syringes 15, 60 and 180 mins after dosing. Equal volumes (0.2ml) from 3 mice were pooled at each time point and 0.6ml of ice-cold ethanol was added. Following chilling at -20°C and centrifugation, 0.5ml of supernatant was dried under reduced pressure. The sample was then reconstituted with 0.5ml of 0.4M NH_4OAc (pH 6.0) and analysed by HPLC.

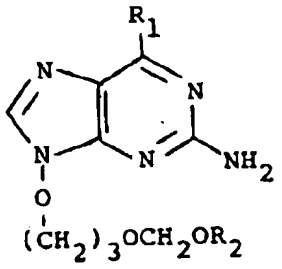
Results

Compound of Example No.	9-(3-Hydroxypropoxy)guanine (E1) conc. (μM) in blood at time (min) after dosing		
	15	60	
1	137	54	Expt. 1
2	36	14	
E1	5.2	2.0	
1	76	12	Expt. 2
3	7.5	4.7	
4	2.1	4.6	
5	7.9	10	
E1	11	3.3	

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein

R_1 is hydrogen or hydroxy; and
R_2 is C_{1-6} alkyl.

2. A compound according to claim 1 wherein R_1 is hydrogen.

3. A compound according to claim 1 or 2 wherein R_2 is iso-propyl.

4. A compound selected from the group consisting of:

2-amino-9-[3-(isopropoxymethoxy)propoxy)purine,

2-amino-9-[3-(methoxymethoxy)propoxy]purine.

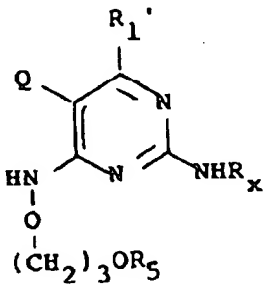
9-[3-(isopropoxymethoxy)propoxy]guanine,

9-[3-(ethoxymethoxy)propoxy]guanine and

2-amino-9-[3-(ethoxymethoxy)propoxy]purine.

5. A process for the preparation of a compound according to claim 1, which process comprises either

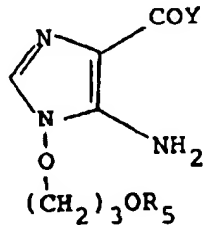
i) imidazole ring closure of a compound of formula (II):



(II)

wherein Q is a group capable of cyclising to form an imidazole ring, such as amino or an amino derivative, for example, formylamino; or

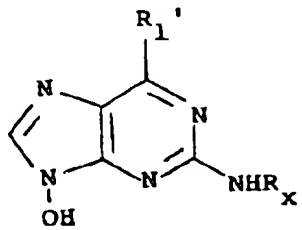
ii) pyrimidine ring closure of a compound of formula (III):



(III)

wherein Y is amino or C_{1-6} alkoxy, with a condensing agent capable of cyclising to form a pyrimidine ring having a 2-NHR_x substituent, resulting in a compound of formula (I) wherein R_1 is hydroxy; or

iii) condensing a compound of formula (IV):



(IV)

with a side chain intermediate of formula (V):

$$R_5O(CH_2)_3Z \qquad (V)$$

wherein Z is a leaving group;
and wherein, in formulae (II) to (V), R_5 is CH_2OR_2 or a group or atom convertible thereto, R_1' is R_1 or a group or atom convertible thereto, R_x is hydrogen or an amino protecting group; and thereafter, when desired or necessary, converting R_5 and/or R_1', when other than CH_2OR_2 and/or R_1, to CH_2OR_2 and/or R_1 respectively, and/or converting R_5 and/or R_1' when CH_2OR_2 and/or R_1 to other CH_2OR_2 and/or R_1 and/or converting R_x when an amino protecting group, to hydrogen.

6. An intermediate of formula (II) as defined in claim 5, wherein R_5 is CH_2OR_2 wherein R_2 is as defined in claim 1.

7. An intermediate compound selected from:

4-[3-(isopropoxymethoxy)propoxyamine and

3-methoxymethoxypropoxyamine.

8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 4, and a pharmaceutically acceptable carrier.

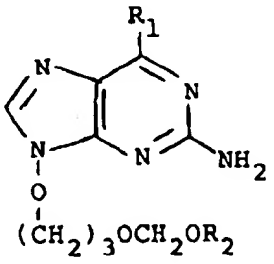
9. A compound according to any one of claims 1 to 4 for use as an active therapeutic substance.

10. A compound according to any one of claims 1 to 4 for use in treating viral infections.

11. Use of a compound according to any one of claims 1 to 4 in the manufacture of a medicament for use in the treatment of viral infections.

Claims for the following Contracting State : ES

1. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



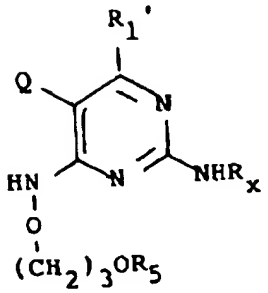
(I)

wherein

R_1 is hydrogen or hydroxy; and
R_2 is C_{1-6} alkyl;

which process comprises either

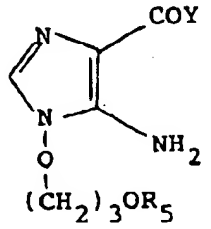
i) imidazole ring closure of a compound of formula (II):



(II)

wherein Q is a group capable of cyclising to form an imidazole ring, such as amino or an amino derivative, for example, formylamino; or

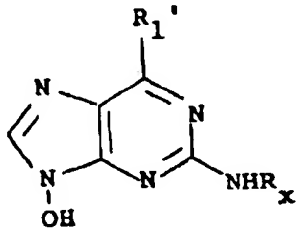
ii) pyrimidine ring closure of a compound of formula (III):



(III)

wherein Y is amino or C_{1-6} alkoxy, with a condensing agent capable of cyclising to form a pyrimidine ring having a 2-NHR_x substituent, resulting in a compound of formula (I) wherein R_1 is hydroxy; or

iii) condensing a compound of formula (IV):



(IV)

with a side chain intermediate of formula (V):

$$R_5O(CH_2)_3Z \qquad (V)$$

wherein Z is a leaving group;

and wherein, in formulae (II) to (V), R_5 is CH_2OR_2 or a group or atom convertible thereto, R_1' is R_1 or a group or atom convertible thereto, R_x is hydrogen or an amino protecting group; and thereafter, when desired or necessary,

converting R_5 and/or R_1', when other than CH_2OR_2 and/or R_1, to CH_2OR_2 and/or R_1 respectively; and/or converting R_5 and/or R_1' when CH_2OR_2 and/or R_1 to other CH_2OR_2 and/or R_1 and/or converting R_x when an amino protecting group, to hydrogen.

2. A process according to claim 1 wherein R_1 is hydrogen.

3. A process according to claim 1 or 2 wherein R_2 is iso-propyl.

4. A process according to claim 1 for the preparation of a compound selected from the group consisting of:

2-amino-9-[3-(isopropoxymethoxy)propoxy)purine,

2-amino-9-[3-(methoxymethoxy)propoxy]purine,

9-[3-(isopropoxymethoxy)propoxy]guanine,

9-[3-(ethoxymethoxy)propoxy]guanine and

2-amino-9-[3-(ethoxymethoxy)propoxy]purine.

5. An intermediate of formula (II) as defined in claim 1, wherein R_5 is CH_2OR_2 wherein R_2 is as defined in claim 1.

6. An intermediate compound selected from:

4-[3-(isopropoxymethoxy)propoxyamine and

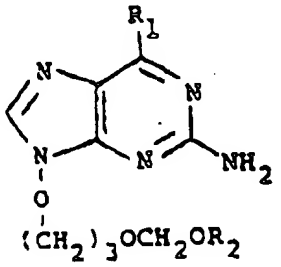
3-methoxymethoxypropoxyamine.

7. Use of a compound of formula (I) as defined in claim 1,in the manufacture of a medicament for use in the treatment of viral infections.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE

1. Verbindung der Formel (I) oder ein pharmazeutisch verträgliches Salz davon:



(I)

in der

R_1 ein Wasserstoffatom oder eine Hydroxylgruppe ist; und
R_2 ein C_{1-6}-Alkylrest ist.

2. Verbindung nach Anspruch 1, in der R_1 ein Wasserstoffatom ist.

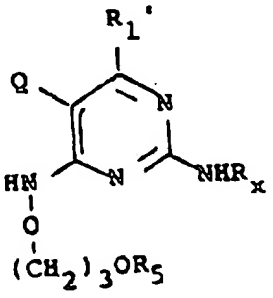
3. Verbindung nach Anspruch 1 oder 2, in der R_2 eine iso-Propylgruppe ist.

4. Verbindung, ausgewählt aus der Gruppe:

2-Amino-9-[3-(isopropoxymethoxy)propoxy]purin,
2-Amino-9-[3-(methoxymethoxy)propoxy]purin,
9-[3-(Isopropoxymethoxy)propoxy]guanin,
9-[3-(Ethoxymethoxy)propoxy]guanin und
2-Amino-9-[3-(ethoxymethoxy)propoxy]purin.

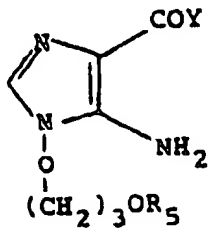
5. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei das Verfahren entweder

i) einen Imidazolringschluß einer Verbindung der Formel (II):



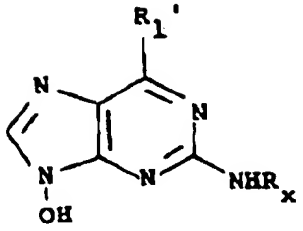
(II)

in der Q ein zur Zyklisierung unter Bildung eines Imidazolrings fähiger Rest, wie eine Aminogruppe oder ein Aminoderivat, zum Beispiel eine Formylaminogruppe, ist; oder
ii) einen Pyrimidinringschluß einer Verbindung der Formel (III):



(III)

in der Y eine Aminogruppe oder ein C_{1-6}-Alkoxyrest ist, mit einem zur Zyklisierung unter Bildung eines Pyrimidinrings fähigen Kondensationsmittel mit einem 2-NHR_x Substituenten, wobei eine Verbindung der Formel (I) erhalten wird, in der R_1 eine Hydroxylgruppe ist;
oder
iii) Kondensation einer Verbindung der Formel (IV):



(IV)

mit einem Seitenkettenzwischenprodukt der Formel (V):

$$R_5O(CH_2)_3Z \qquad (V)$$

in der Z eine Abgangsgruppe ist;

und wobei in den Formeln (II) bis (V) R_5 CH_2OR_2 oder ein dazu umwandelbarer Rest oder Atom ist, R_1' R_1 oder ein dazu umwandelbarer Rest oder Atom ist, R_x ein Wasserstoffatom oder eine Aminoschutzgruppe ist; und anschließend, falls gewünscht oder erforderlich, Umwandeln von R_5 und/oder R_1', wenn sie andere Reste als CH_2OR_2 und/oder R_1 sind, in jeweils CH_2OR_2 und/oder R_1, und/oder Umwandeln von R_5 und/oder R_1', wenn sie CH_2OR_2 und/oder R_1 sind, in andere Reste CH_2OR_2 und/oder R_1 und/oder Umwandeln von R_x, wenn es eine Aminoschutzgruppe ist, in ein Wasserstoffatom, umfaßt.

6. Zwischenprodukt der Formel (II) nach Anspruch 5, in dem R_5 CH_2OR_2 ist, wobei R_2 die in Anspruch 1 angegebene Bedeutung hat.

7. Zwischenprodukt, ausgewählt aus

   4-[3-(Isopropoxymethoxy)propoxy]amin und
   3-Methoxymethoxypropoxyamin.

8. Arzneimittel, umfassend eine Verbindung nach einem der Ansprüche 1 bis 4 und einen pharmazeutisch verträglichen Träger.

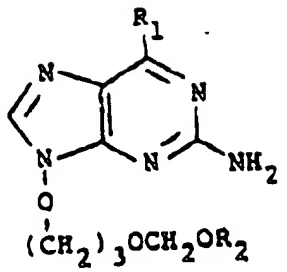
9. Verbindung nach einem der Ansprüche 1 bis 4 zur Verwendung als therapeutischen Wirkstoff.

10. Verbindung nach einem der Ansprüche 1 bis 4 zur Verwendung bei der Behandlung von Virusinfektionen.

11. Verwendung einer Verbindung nach einem der Ansprüche 1 bis 4 zur Herstellung eines Medikaments zur Verwendung bei der Behandlung von Virusinfektionen.

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Verbindung der Formel (I) oder eines pharmazeutisch verträglichen Salzes davon:



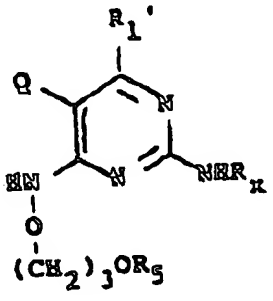
(I)

wobei

R_1 ein Wasserstoffatom oder eine Hydroxylgruppe ist; und
R_2 ein C_{1-6}-Alkylrest ist;

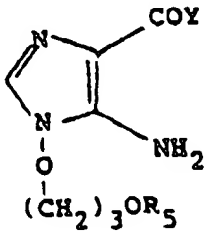
wobei das Verfahren entweder

i) einen Imidazolringschluß einer Verbindung der Formel (II):



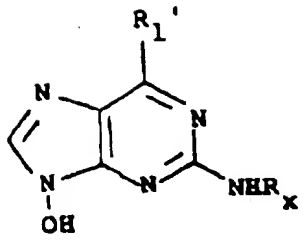
(II)

in der Q ein zur Zyklisierung unter Bildung eines Imidazolrings fähiger Rest, wie eine Aminogruppe oder ein Aminoderivat, zum Beispiel eine Formylaminogruppe, ist; oder
ii) einen Pyrimidinringschluß einer Verbindung der Formel (III):



(III)

in der Y eine Aminogruppe oder ein C_{1-6}-Alkoxyrest ist, mit einem zur Zyklisierung unter Bildung eines Pyrimidinrings fähigen Kondensationmittel mit einem 2-NHR_x Substituenten, wobei eine Verbindung der Formel (I) erhalten wird, in der R_1 eine Hydroxylgruppe ist;
oder
iii) Kondensation einer Verbindung der Formel (IV):



(IV)

mit einem Seitenkettenzwischenprodukt der Formel (V):

$$R_5O(CH_2)_3Z \qquad (V)$$

in der Z eine Abgangsgruppe ist;

und wobei in den Formeln (II) bis (V) R_5 CH_2OR_2 oder ein dazu umwandelbarer Rest oder Atom ist, R_1' R_1 oder ein dazu umwandelbarer Rest oder Atom ist, R_x ein Wasserstoffatom oder eine Aminoschutzgruppe ist; und anschließend, falls gewünscht oder erforderlich, Umwandeln von R_5 und/oder R_1', wenn sie andere Reste als CH_2OR_2 und/oder R_1 sind, in jeweils CH_2OR_2 und/oder R_1, und/oder Umwandeln von R_5 und/oder R_1, wenn sie CH_2OR_2 und/oder R_1 sind, in andere Reste CH_2OR_2 und/oder R_1 und/oder Umwandeln von R_x, wenn es eine Aminoschutzgruppe ist, in ein Wasserstoffatom, umfaßt.

2. Verfahren nach Anspruch 1, wobei R_1 ein Wasserstoffatom ist.

3. Verfahren nach Anspruch 1 oder 2, wobei R_2 eine iso-Propylgruppe ist.

4. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung, ausgewählt aus der Gruppe:

   2-Amino-9-[3-(isopropoxymethoxy)propoxy]purin,
   2-Amino-9-[3-(methoxymethoxy)propoxy]purin,
   9-[3-(isopropoxymethoxy)propoxy]guanin,
   9-[3-(Ethoxymethoxy)propoxy]guanin und
   2-Amino-9-[3-(ethoxymethoxy)propoxy]purin.

5. Zwischenprodukt der Formel (II) nach Anspruch 1, in dem R_5 CH_2OR_2 ist, wobei R_2 die in Anspruch 1 angegebene Bedeutung hat.

6. Zwischenprodukt, ausgewählt aus

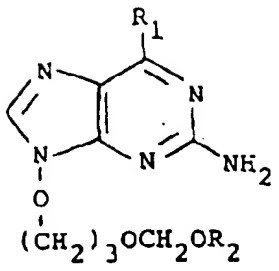
   4-[3-(Isopropoxymethoxy)propoxy]amin und
   3-Methoxymethoxypropoxyamin.

7. Verwendung einer Verbindung der Formel (I) nach Anspruch 1 zur Herstellung eines Arzneimittels zur Verwendung bei der Behandlung von Virusinfektionen.

Revendications

Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, GR, IT, LI, LU, NL, SE

1. Composé de formule (I) ou un de ses sels pharmaceutiquement acceptables :



(I)

formule dans laquelle

R_1 représente l'hydrogène ou un groupe hydroxy ;
et R_2 représente un groupe alkyle en C_1 à C_6.

2. Composé suivant la revendication 1, dans lequel R_1 représente l'hydrogène.

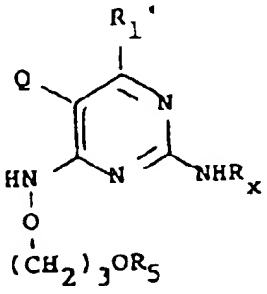
3. Composé suivant la revendication 1 ou 2 , dans lequel R_2 représente un groupe isopropyle.

4. Composé choisi dans le groupe consistant en :

2-amino-9-[3-(isopropoxyméthoxy)propoxy)purine,
2-amino-9-[3-(méthoxyméthoxy)propoxy)purine,
9-[3-(isopropoxyméthoxy)propoxy)guanine,
9-[3-(éthoxyméthoxy)propoxy)guanine, et
2-amino-9-[3-(éthoxyméthoxy)propoxy)purine.

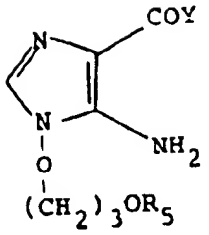
5. Procédé pour la préparation d'un composé suivant la revendication 1, procédé qui comprend

i) la cyclisation, formant un noyau imidazole, d'un composé de formule (II) :



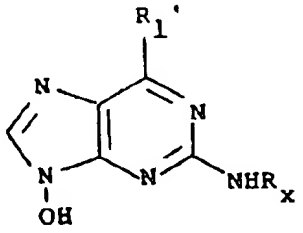
(II)

dans laquelle Q représente un groupe apte à la cyclisation pour former un noyau imidazole, tel qu'un groupe amino ou un dérivé à fonction amino, par exemple un groupe formylamino ; ou
ii) la cyclisation, formant un noyau pyrimidine, d'un composé de formule (III) :



(III)

dans laquelle Y représente un groupe amino ou alkoxy en C_1 à C_6, avec un agent de condensation aple à la cyclisation pour former un noyau pyrimidine ayant un substituant 2-NHR_x, avec pour résultat un composé de formule (I) dans laquelle R_1 représente un groupe hydroxy :
ou
iii) la condensation d'un composé de formule (IV) :



(IV)

avec un intermédiaire de chaîne latérale de formule (V) :

$$R_5O(CH_2)_3Z \qquad (V)$$

dans laquelle Z représente un groupe partant ;

procédé dans lequel, dans les formules (II) à (V), R_5 représente un groupe CH_2OR_2 ou un groupe ou atome pouvant être transformé en ce groupe, R_1' représente un groupe R_1 ou un groupe ou atome pouvant être transformé en ce groupe, R_x représente l'hydrogène ou un groupe protecteur de la fonction amino ; puis, lorsque cela est désiré ou nécessaire, la transformation de R_5 et/ou R_1', lorsqu'ils représentent des groupes autres que CH_2OR_2 et/ou R_1, respectivement en des groupes CH_2OR_2 et/ou R_1, et/ou la transformation de R_5 et/ou R_1', lorsqu'ils représentent des groupes CH_2OR_2 et/ou R_1, en d'autres groupes CH_2OR_2 et/ou R_1, et/ou la transformation de R_x, lorsqu'il représente un groupe protecteur de la fonction amino, en l'hydrogène.

6. Intermédiaire de formule (II) répondant à la définition suivant la revendication 5, dans lequel R_5 représente un groupe CH_2OR_2 dans lequel R_2 répond à la définition suivant la revendication 1.

7. Composé intermédiaire choisi entre :

la 4-[3-(isopropoxyméthoxy)propoxyamine, et
la 3-méthoxyméthoxypropoxyamine.

8. Composition pharmaceutique comprenant un composé suivant l'une quelconque des revendications 1 à 4 et un support pharmaceutiquement acceptable.

9. Composé suivant l'une quelconque des revendications 1 à 4, destiné à être utilisé comme substance thérapeutique

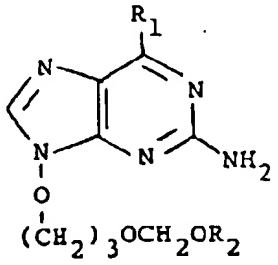
active.

10. Composé suivant l'une quelconque des revendications 1 à 4, destiné à être utilisé dans le traitement d'infections virales.

11. Utilisation d'un composé suivant l'une quelconque des revendications 1 à 4 dans la production d'un médicament destiné à être utilisé dans le traitement d'infections virales.

Revendications pour l'Etat contractant suivant : ES

1. Procédé pour la préparation d'un composé de formule (I) ou d'un de ses sels pharmaceutiquement acceptables :



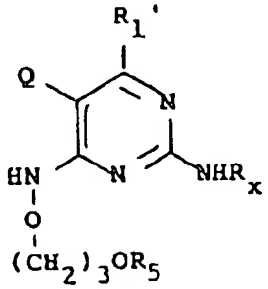
(I)

formule dans laquelle

R_1 représente l'hydrogène ou un groupe hydroxy ;
et R_2 représente un groupe alkyle en C_1 à C_6 ;

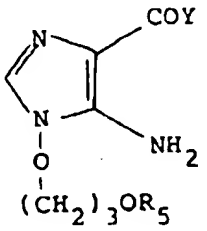
procédé qui comprend

i) la cyclisation, formant un noyau imidazole, d'un composé de formule (II) :



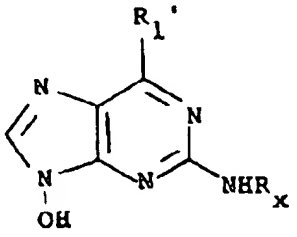
(II)

dans laquelle Q représente un groupe apte à la cyclisation pour former un noyau imidazole, tel qu'un groupe amino ou un dérivé à fonction amino, par exemple un groupe formylamino ; ou
ii) la cyclisation, formant un noyau pyrimidine, d'un composé de formule (III) :



(III)

dans laquelle Y représente un groupe amino ou alkoxy en C_1 à C_6, avec un agent de condensation apte à la cyclisation pour former un noyau pyrimidine ayant un substituant 2-NHR_x, avec pour résultat un composé de formule (I) dans laquelle R_1 représente un groupe hydroxy ;
ou
iii) la condensation d'un composé de formule (IV) :



(IV)

avec un intermédiaire de chaîne latérale de formule (V) :

$$R_5O(CH_2)_3Z \qquad (V)$$

dans laquelle Z représente un groupe partant ;

procédé dans lequel, dans les formules (II) à (V), R_5 représente un groupe CH_2OR_2 ou un groupe ou atome pouvant être transformé en ce groupe, R_1' représente un groupe R_1 ou un groupe ou atome pouvant être transformé en ce groupe, R_x représente l'hydrogène ou un groupe protecteur de la fonction amino ; puis, lorsque cela est désiré ou nécessaire, la transformation de R_5 et/ou R_1', lorsqu'ils représentent des groupes autres que CH_2OR_2 et/ou R_1, respectivement en des groupes CH_2OR_2 et/ou R_1, et/ou la transformation de R_5 et/ou R_1', lorsqu'ils représentent des groupes CH_2OR_2 et/ou R_1, en d'autres groupes CH_2OR_2 et/ou R_1, et/ou la transformation de R_x, lorsqu'il représente un groupe protecteur de la fonction amino, en l'hydrogène.

2. Procédé suivant la revendication 1, dans lequel R_1 représente l'hydrogène.

3. Procédé suivant la revendication 1 ou 2, dans lequel R_2 représente un groupe isopropyle.

4. Procédé suivant la revendication 1 pour la préparation d'un composé choisi dans le groupe consistant en :

2-amino-9-[3-(isopropoxyméthoxy)propoxy)purine,
2-amino-9-[3-(méthoxyméthoxy)propoxy)purine,
9-[3-(isopropoxyméthoxy)propoxy)guanine,
9-[3-(éthoxyméthoxy)propoxy)guanine, et
2-amino-9-[3-(éthoxyméthoxy)propoxy)purine.

5. Intermédiaire de formule (II) répondant à la définition suivant la revendication 1, dans lequel R_5 représente un

groupe CH_2OR_2 dans lequel R_2 répond à la définition suivant la revendication 1.

6. Composé intermédiaire choisi entre :

la 4-[3-(isopropoxyméthoxy)propoxyamine, et
la 3-méthoxyméthoxypropoxyamine.

7. Utilisation d'un composé de formule (I) répondant à la définition suivant la revendication 1 dans la production d'un médicament destiné à être utilisé dans le traitement d'infections virales.